

Acute Hemodynamic and Neurohumoral Effects of Selective ET_A Receptor Blockade in Patients With Congestive Heart Failure

Lukas E. Spieker, MD, Veselin Mitrovic, MD,* Georg Noll, MD, FESC, Richard Pacher, MD,† Matthias R. Schulze, MD,‡ Jörg Muntwyler, MD, MPH, Christoph Schalcher, MD, Wolfgang Kiowski, MD, FACC, FESC, Thomas F. Lüscher, MD, FACC, FRCP, FESC, on behalf of the ET 003 Investigators

Zurich, Switzerland; Bad Nauheim and Dresden, Germany; and Wien, Austria

- OBJECTIVES** To investigate the hemodynamic effects of the selective endothelin (ET)_A receptor antagonist LU135252 in patients with congestive heart failure (CHF).
- BACKGROUND** Nonselective ET_{A/B} receptor antagonists improve hemodynamics in patients with CHF. Since ET_B receptors mediate the release of nitric oxide and the clearance of ET-1, selective ET_A antagonists are of special interest.
- METHODS** The hemodynamic effects of a single oral dose of the selective ET_A receptor antagonist LU135252 (1, 10, 30, 100 or 300 mg) were investigated in a multicenter study involving 95 patients with CHF (New York Heart Association II–III) with an ejection fraction $\leq 35\%$.
- RESULTS** Baseline ET-1 positively correlated with pulmonary vascular resistance, pulmonary capillary wedge pressure (PCWP), and mean pulmonary artery pressure (MPAP, $r = 0.37$ – 0.50 , $p < 0.0004$) but were inversely related to cardiac index (CI; $r = -0.36$, $p = 0.0004$). LU135252 dose dependently increased CI and decreased mean arterial pressure and systemic vascular resistance ($p < 0.03$ – 0.0002), while heart rate remained constant or decreased slightly. Pulmonary capillary wedge pressure, MPAP, pulmonary vascular resistance and right atrial pressure also decreased significantly ($p < 0.035$ – < 0.0001). Two hours after LU135252, plasma ET-1 did not significantly increase after 1 mg but did so by 23% ($p = 0.003$), 29% ($p = 0.0018$), 56% ($p < 0.0001$) and 101% ($p < 0.0001$) after 10, 30, 100 and 300 mg, respectively, while plasma catecholamines remained constant.
- CONCLUSIONS** In patients with CHF, a single oral dose of the selective ET_A receptor antagonist LU135252 improves hemodynamics in a dose-dependent manner without activation of other neurohumoral systems and is well tolerated over a wide dose range. (J Am Coll Cardiol 2000;35:1745–52) © 2000 by the American College of Cardiology

The vascular endothelium produces and releases endothelin (ET)-1, nitric oxide (NO) and prostacyclin and, thereby, plays a fundamental role in the regulation of vascular tone and structure (1–3). Endothelin_A and ET_B receptors mediate the vasoconstrictor effects of ET-1 in smooth muscle cells (4–6). Endothelin-1 also induces proliferation of vascular smooth muscle cells and myocardial hypertrophy (7–9). In contrast, endothelial ET_B receptors cause vasodilation via release of NO and prostacyclin, which also exert antithrombotic and antiproliferative effects in vascular smooth muscle cells (10–12). Further, ET_B receptors in the

pulmonary circulation are important for the clearance of ET-1 (13–16).

Increased peripheral resistance is a key feature of congestive heart failure (CHF). Apart from activation of neurohormonal systems—such as the sympathetic nervous system (13) and the renin angiotensin system (14)—there is evidence that increased ET-1 production contributes to vasoconstriction as well. Indeed, plasma levels of ET-1 are elevated, and plasma levels of the precursor of ET-1, big ET-1, are strong, independent predictors of death in patients with heart failure (15–17). In experimental heart failure of the rat, ET_A receptor blockade improves survival (18). In patients with CHF, nonselective ET_{A/B} blockade improves pulmonary and systemic hemodynamics (19,20).

Although there are good reasons to develop ET receptor antagonists for the treatment of CHF, it remains controversial whether nonselective ET_{A/B} receptor antagonists or

From the Division of Cardiology, University Hospital, Zürich, Switzerland; the *Kerckhoff Clinic, Bad Nauheim, Germany; the †Allgemeines Krankenhaus, Wien, Austria; and the ‡Herz-und Kreislaufzentrum, Cardiology, Dresden, Germany. This study was supported by Knoll Pharmaceuticals, Ludwigshafen, Germany.

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Abbreviations and Acronyms

CHF	= congestive heart failure
CI	= cardiac index
ET	= endothelin
MPAP	= mean pulmonary artery pressure
NO	= nitric oxide
PCWP	= pulmonary capillary wedge pressure

selective ET_A receptor antagonists should be used. Since ET_B receptors stimulate the release of NO, which is impaired in heart failure (21), and are also involved in the pulmonary clearance of ET-1 (22–25), selective ET_A receptor antagonists are of particular interest. We investigated the hemodynamic and neurohumoral effects of a single oral dose of LU135252, a selective ET_A endothelin receptor antagonist, in patients with CHF.

METHODS

Patients. A total of 100 patients with CHF with an ejection fraction $\leq 35\%$ as assessed by echocardiography or isotope ventriculography of any underlying cause (except primary organic valvular heart disease) participated in a prospective multicenter trial (for centers see Acknowledgments). Each patient gave written, informed consent, and this study was approved by the local ethical committees of each of the participating centers.

Inclusion and exclusion criteria. The following baseline criteria had to be met for inclusion: pulmonary capillary wedge pressure (PCWP) ≥ 14 mm Hg or cardiac index (CI) ≤ 2.8 l/min/m². Exclusion criteria were acutely decompensated heart failure (New York Heart Association IV), sustained or symptomatic systemic hypotension (systolic blood pressure ≤ 90 mm Hg), acute myocardial infarction within three months before study enrollment, unstable angina pectoris, primary valvular heart disease, continued pacemaker rhythm, stroke within six months before study enrollment, introduction of beta-adrenergic blocking agent therapy within three months before study enrollment, pregnancy or lactation, liver disease, renal failure (creatinine > 220 μ mol/l) and exposure to any investigational drug during the last month before study entry.

Experimental protocol. Patients continued their usual medications except on the investigational day. All drugs with impact on hemodynamic parameters were discontinued the morning of the study. Different open-label dosage levels (1, 10, 30, 100 and 300 mg) were studied in different patient groups.

After recording stable hemodynamic baseline values for 30 min, LU135252 was administered orally with 200 ml water. Arterial blood pressure and hemodynamic variables were measured at 30, 60, 90, 120, 180 and 240 min after oral administration of the drug. Blood samples were drawn

Table 1. Main Demographic and Hemodynamic Data of the Study Patients (n = 95)

Age (yrs)	56.9 \pm 10.6
Gender (male/female)	86/9
Weight (kg)	78.1 \pm 13.2
Height (m)	1.73 \pm 0.07
BMI (kg·m ⁻²)	26.1 \pm 3.6
Systolic blood pressure (mm Hg)	125 \pm 20
Diastolic blood pressure (mm Hg)	76 \pm 14
Heart rate (min ⁻¹)	73 \pm 15
Cardiac index (ml·min ⁻¹ ·m ⁻²)	2.3 \pm 0.4
Systemic vascular resistance (dyn·s ⁻¹ ·cm ⁻⁵)	1,570 \pm 388
Right atrial pressure (mm Hg)	7 \pm 4
Mean pulmonary artery pressure (mm Hg)	30 \pm 12
Pulmonary capillary wedge pressure (mm Hg)	19 \pm 7
Pulmonary vascular resistance (dyn·s ⁻¹ ·cm ⁻⁵)	204 \pm 160

Values represent means \pm standard deviation.

BMI = body mass index.

from the atrial part of the Swan-Ganz catheter or a peripheral vein shortly before the hemodynamic measurements. Electrocardiographic monitoring was performed throughout the entire investigational period. Four hours after administration of LU135252, the Swan-Ganz catheter was withdrawn. For safety reasons, the patients spent the following night in the hospital.

Hemodynamic measurements. Cardiac output (average of at least two measurements) was determined by thermodilution with a Swan-Ganz catheter inserted through a sheath introducer system in a jugular or cubital vein and propagated to the pulmonary artery. Right atrial pressure, systemic and pulmonary artery pressure and PCWP were measured. Cardiac index and systemic and pulmonary vascular resistance were calculated using standard formula. Heart rate was obtained from electrocardiogram monitoring.

Determination of plasma levels. Blood samples were drawn at baseline and 30, 60, 90, 120, 180 and 240 min after administration of LU135252. Plasma, obtained by centrifugation, was stored at -70°C until analysis. Plasma levels of ET-1 and catecholamines were assayed 15 min before and 120 and 240 min after administration of the study drug using methodology described previously (26–28). Plasma norepinephrine in healthy subjects averaged 208 ± 75 pg/ml with the assay used. The concentration of ET-1 in plasma from healthy control subjects with this assay was 2.8 ± 0.5 pg/ml (27).

Statistical analysis. Means and proportion of baseline characteristics were calculated overall and by treatment assignment. The average mean change of the hemodynamic variables at 120, 180 and 240 min according to treatment assignment was estimated with repeated-measurement analysis of covariance, adjusting for the respective baseline values and assuming compound symmetry among the three time categories (SAS PROC MIXED). For all hemodynamic parameters, time and time*dose interaction was not

Table 2. Concomitant Cardiovascular Drugs of the Study Patients

Angiotensin-converting enzyme inhibitor	93% (n = 88)
Diuretic	86% (n = 82)
Digoxin	68% (n = 65)
Nitrate	53% (n = 50)
Aspirin	42% (n = 40)
Beta-blocker	39% (n = 37)
Cordarone	28% (n = 27)
Oral anticoagulant	27% (n = 26)
Statin	16% (n = 15)
Angiotensin II antagonist	12% (n = 11)
Calcium antagonist	8% (n = 8)
Fibrate	3% (n = 3)

significant. For the estimated changes of the five treatment doses, statistical significance was assumed at a Bonferroni-adjusted p value of $<0.05/5 = 0.01$. To test the dose-response effect, dose was entered as an ordinal variable into the model, and significance was defined as an alpha level of <0.05 .

RESULTS

Patients' characteristics and medication. Five of the 100 patients entering the study were excluded because they did not fulfill the hemodynamic inclusion criteria or because they met one or more exclusion criteria. Baseline demographic and hemodynamic characteristics of the 95 study patients are shown in Table 1. The concomitant cardiovascular medication of the study patients is listed in Table 2.

Plasma endothelin and hemodynamics at baseline. Baseline hemodynamics at baseline according to treatment group are shown in Table 3. Baseline ET-1 averaged 2.7 ± 0.1 pg/ml (range 1.3–7.9 pg/ml). Baseline ET-1 plasma levels positively correlated with pulmonary vascular resistance ($r = 0.50$, $p < 0.0001$), PCWP ($r = 0.37$, $p = 0.004$), mean pulmonary artery pressure (MPAP) ($r = 0.46$, $p < 0.0001$), systemic vascular resistance ($r = 0.21$, $p = 0.051$) and right atrial pressure ($r = 0.22$, $p = 0.03$; Fig. 1). In

contrast, ET-1 levels were inversely related to CI ($r = -0.36$, $p = 0.0004$). Baseline ET-1 levels were not correlated with heart rate nor with systemic mean arterial pressure. The correlation between hemodynamic parameters was not altered by exclusion of the single patient with a very high ET plasma level and remained highly significant (correlation between ET-1 plasma levels and MPAP, $r = 0.42$, $p < 0.0001$; PCWP, $r = 0.34$, $p = 0.001$; CI, $r = 0.34$, $p = 0.001$).

Hemodynamic effects. ARTERIAL CIRCULATION. The hemodynamic changes after administration of LU135252 are shown in Table 4. LU135252 led to a dose-dependent increase in CI. The average mean increases in CI after 1, 10, 30, 100 or 300 mg of LU135252, respectively, were +8%, +11% (both NS), +13% ($p < 0.01$), +19% ($p < 0.01$) and 22% ($p < 0.01$). Mean arterial pressure decreased by 5%, 5%, 3%, 5% and 10% ($p < 0.01$ for all dosages). Accordingly, systemic vascular resistance decreased dose dependently by 11% to 27% ($p < 0.01$ for all dosages except 1 mg). Importantly, heart rate remained stable. After 24 h, LU135252 still reduced arterial blood pressure by -5% ($p = 0.06$), -6% ($p = 0.016$), 0.1% (NS), -15% ($p = 0.008$) and -10% ($p = 0.0016$). The lack of a strict dose dependency of the blood pressure lowering effect is explained by accidental, nonsignificant differences in the baseline blood pressure between the dosage groups (Table 3).

PULMONARY CIRCULATION. The changes in pulmonary hemodynamics after administration of LU135252 are shown in Table 4. Right atrial pressure was reduced by 12% to 19% ($p < 0.01$ for 30 and 100 mg). Mean pulmonary artery pressure decreased by 10% to 20% ($p < 0.01$ for all dosages except 1 mg). Pulmonary capillary wedge pressure was reduced by 15% to 25% ($p < 0.01$). Pulmonary vascular resistance dose dependently decreased by 6% to 26% ($p < 0.01$ for 100 and 300 mg).

Endothelin plasma levels after ET_A blockade. Two hours after LU135252, plasma ET-1 dose dependently increased

Table 3. Baseline Hemodynamic Parameters According to Treatment Group

	LU135252 Dose					p Value
	1 mg	10 mg	30 mg	100 mg	300 mg	
CI (l/min)	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.5	2.4 ± 0.4	2.1 ± 0.4	0.32
HR (beats/min)	72 ± 16	72 ± 15	73 ± 19	77 ± 12	70 ± 14	0.72
MAP (mm Hg)	92 ± 11	92 ± 16	87 ± 15	97 ± 15	87 ± 10	0.16
SVR ($\text{dyn}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$)	$1,637 \pm 343$	$1,632 \pm 409$	$1,423 \pm 401$	$1,621 \pm 379$	$1,558 \pm 393$	0.36
RAP (mm Hg)	8.6 ± 4.6	6.3 ± 3.0	7.4 ± 3.8	7.3 ± 5.6	7.1 ± 3.6	0.63
MPAP (mm Hg)	30 ± 11	29 ± 10	30 ± 14	32 ± 12	29 ± 11	0.91
PCWP (mm Hg)	21 ± 9	19 ± 8	19 ± 6	19 ± 5	18 ± 7	0.87
PVR ($\text{dyn}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$)	183 ± 91	166 ± 85	208 ± 205	247 ± 207	205 ± 140	0.58

Values represent means \pm SD.

CI = cardiac index; HR = heart rate; MAP = mean systemic arterial pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SVR = systemic vascular resistance.

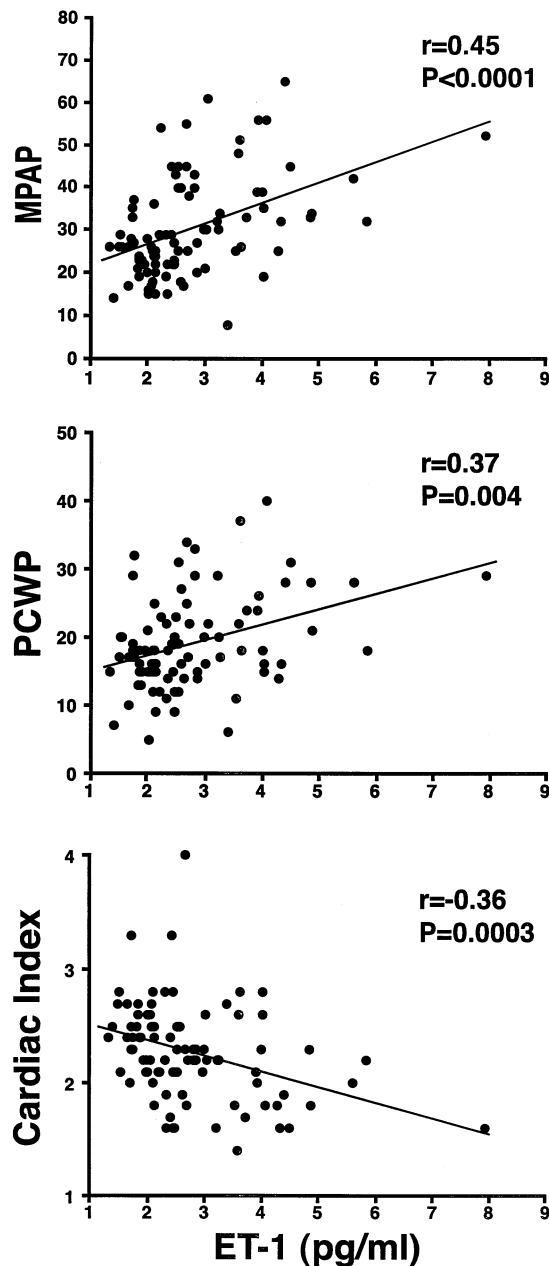


Figure 1. Correlations between baseline endothelin (ET)-1 plasma levels and hemodynamic parameters in patients with chronic heart failure ($n = 91$). Mean pulmonary artery (MPAP, mm Hg; top) and pulmonary capillary wedge pressure (PCWP, mm Hg; middle) correlated positively with ET-1 plasma levels, while cardiac index (ml·min⁻¹·m⁻²; bottom) was inversely associated with ET-1 levels.

by 6% after administration of 1 mg of the ET_A antagonist ($p = 0.47$), by 23% after 10 mg ($p = 0.003$), by 29% after 30 mg ($p = 0.002$), by 56% after 100 mg ($p < 0.0001$) and by 101% after 300 mg ($p < 0.0001$), respectively (Fig. 3).

Plasma catecholamines. Baseline plasma norepinephrine levels averaged 531 ± 78 ng/ml and baseline epinephrine levels 56 ± 6 ng/ml.

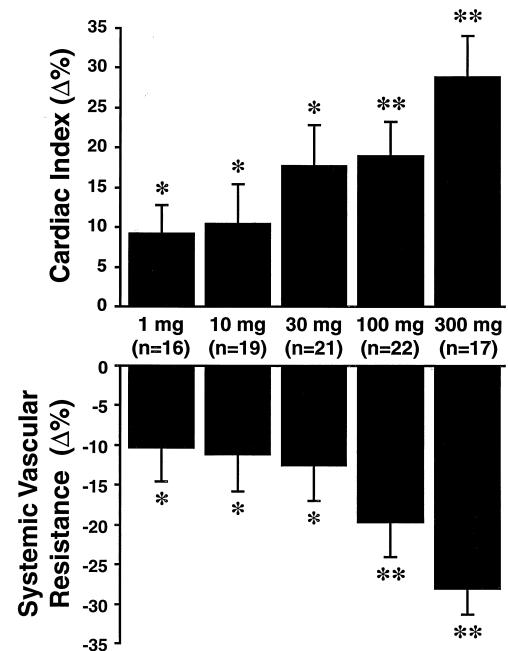


Figure 2. Changes of cardiac index and systemic vascular resistance 4 h after administration of different dosages of LU135252, a selective ET_A receptor antagonist. * $p < 0.05$; ** $p \leq 0.0002$.

Baseline norepinephrine plasma levels positively correlated with pulmonary vascular resistance ($r = 0.49$, $p < 0.0001$), with systemic vascular resistance ($r = 0.31$, $p = 0.01$), with mean arterial blood pressure ($r = 0.29$, $p = 0.016$), with MPAP ($r = 0.47$, $p < 0.0001$), with PCWP ($r = 0.32$, $p = 0.009$) and with right atrial pressure ($r = 0.38$, $p = 0.0016$) but not with CI ($r = -0.21$, $p = 0.09$) nor heart rate ($r = 0.18$, $p = 0.15$). Norepinephrine plasma levels were positively correlated with ET-1 plasma levels ($r = 0.57$, $p = 0.004$).

Epinephrine plasma levels only correlated with PCWP ($r = 0.41$, $p = 0.0006$) and with MPAP ($r = 0.34$, $p = 0.005$) but not with the other hemodynamic parameters. Also, there was no significant correlation between epinephrine and ET-1 plasma levels. Epinephrine, however, correlated with norepinephrine levels ($r = 0.62$, $p = 0.023$).

Plasma catecholamines remained stable or decreased slightly after administration of LU135252.

Plasma levels of LU135252. Plasma levels of the selective ET_A receptor antagonist LU135252 increased dose dependently after single oral administration of various dosages. Peak plasma levels occurred between 120 and 180 min after administration (at 180 min: 31 ± 4 ng/ml after 1 mg, 430 ± 40 after 10 mg, $1,006 \pm 103$ ng/ml after 30 mg, $4,092 \pm 560$ ng/ml after 100 mg and $14,266 \pm 1,221$ ng/ml after 300 mg; $p_{\text{trend}} < 0.0001$) and remained elevated over 24 h ($p_{\text{trend}} < 0.0001$).

Safety. Fourteen adverse events were recorded in the patients receiving LU135252 (Table 5): one patient developed

Table 4. Mean Hemodynamic Baseline Values and Absolute Changes According to Treatment

	Baseline	LU135252 Dose					P _{trend}
		1 mg	10 mg	30 mg	100 mg	300 mg	
CI (l/min)	2.28 ± 0.04	0.18 ± 0.08	0.24 ± 0.10	0.30 ± 0.08*	0.44 ± 0.10*	0.50 ± 0.09*	<0.001
HR (beats/min)	73.2 ± 1.5	-3.3 ± 2.0	0.1 ± 1.9	-1.5 ± 1.7	-2.0 ± 1.2	-0.2 ± 1.5	0.55
MAP (mm Hg)	91.2 ± 1.4	-4.6 ± 1.2*	-4.5 ± 1.4*	-3.1 ± 1.5*	-5.0 ± 1.5*	-8.7 ± 1.4*	0.09
SVR (dyn·s ⁻¹ ·cm ⁻⁵)	1,570 ± 40	-169 ± 35	-165 ± 57*	-207 ± 63*	-317 ± 56*	-424 ± 52*	<0.001
RAP (mm Hg)	7.3 ± 0.4	-0.9 ± 0.5	-1.2 ± 0.3	-1.4 ± 0.4*	-1.3 ± 0.4*	-1.1 ± 0.6	0.81
MPAP (mm Hg)	30.1 ± 1.2	-3.0 ± 1.0	-5.1 ± 1.1*	-5.1 ± 1.4*	-6.0 ± 0.8*	-4.0 ± 1.1*	0.47
PCWP (mm Hg)	19.0 ± 0.7	-2.8 ± 1.1*	-4.7 ± 1.0*	-4.2 ± 0.7*	-4.8 ± 0.7*	-3.1 ± 0.9*	0.86
PVR (dyn·s ⁻¹ ·cm ⁻⁵)	204 ± 16	-12 ± 11	-25 ± 12	-24 ± 17	-49 ± 10*	-53 ± 13*	<0.02

Values are means ± SE and represent the average mean responses at 120, 180 and 240 min, adjusted for baseline levels.

*Significant change vs. baseline (Bonferroni-adjusted alpha-level of 0.01).

CI = cardiac index; HR = heart rate; MAP = mean systemic arterial pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SVR = systemic vascular resistance.

hypotension after 30 mg of LU135252 and one patient developed markedly elevated pulmonary artery pressure (71/38 mm Hg, mean 51 mm Hg) pulmonary edema (after 10 mg). Four cases (5.3%) of mild to moderate headache occurred. In two patients bilirubin levels increased (four-fold and two-fold) without increases in liver transaminases and alkaline phosphatase. One case of ventricular tachycardia was classified as unlikely to be related to the study medication. One patient had a decrease in platelet count (from 371'000 to 128'000 ml⁻¹) 15 min before administration of the study drug, which spontaneously normalized 4 h later (to 255'000 ml⁻¹). The same patient experienced a headache and a decrease in activated partial prothrombin time 240 min after the study drug, which also normalized spontaneously. One case of neck pain, one case of high glucose and one case of preexisting anemia were classified as unrelated. All patients recovered without sequelae.

DISCUSSION

This study demonstrates that a single oral dose of the selective ET_A receptor antagonist LU135252 has marked beneficial hemodynamic effects in patients with chronic heart failure. Cardiac index increased, while systemic vascular resistance decreased in a dose-dependent manner, as did pulmonary vascular resistance. Importantly, these favorable effects occurred in the absence of neurohormonal stimulation or increases of heart rate. The improvement in hemodynamics was comparable with that observed with nonselective ET_{A/B} receptor antagonists but was accompanied by a smaller increase in ET-1 plasma levels (23,24). The results substantiate the concept that ET-1 importantly contributes to increased peripheral resistance and to the decrease in cardiac output in chronic heart failure.

Hemodynamic effects of selective ET_A antagonism in heart failure. Increased peripheral resistance is a key feature of CHF that further impairs cardiac performance. Vasoconstriction is a consequence of the activation of several neurohormonal systems, e.g., the sympathetic ner-

vous system (13,29) and the renin angiotensin system (18). In line with this concept, ET-1 plasma levels are elevated in heart failure patients and correlate with hemodynamic severity (15,17,19,30,31). Also, in this large population of patients with CHF, we found a close positive relation of ET-1 plasma levels with systemic and pulmonary pressures and resistances and an inverse relation to cardiac output. In this study, LU135252 led to venous, pulmonary and arterial vasodilation and caused a pronounced increase in cardiac output. There were no signs of an activation of the sympathetic nervous system after administration of LU135252. Indeed, both plasma catecholamine levels and heart rate remained stable in spite of the marked hemodynamic effects. The hemodynamic effects of LU135252 as well as the presence of the compound in plasma lasted for approximately 24 h. The dose dependency of the effects of LU135252 on CI and pulmonary vascular resistance was

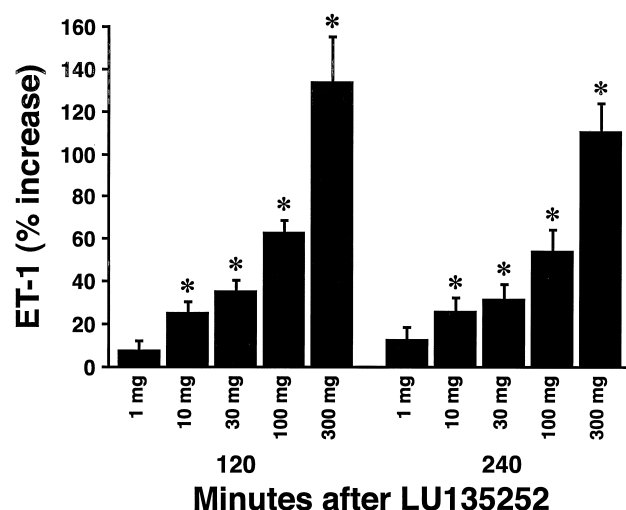


Figure 3. Changes of endothelin-1 plasma levels after administration of various dosages of the selective ET_A receptor antagonist LU135252. There was a dose-dependent increase in plasma ET-1 levels. *p < 0.003 vs. baseline.

Table 5. Adverse Events

Adverse Event	Observed Frequency	Relation to Study Medication
Headache	4.2% (n = 4)	probable (2), possible (1), unrelated (1)
Increased bilirubin	2.1% (n = 2)	possible
Hypotension	1.1% (n = 1)	possible
Pulmonary edema	1.1% (n = 1)	unlikely
Ventricular tachycardia	1.1% (n = 1)	unlikely
Neck pain	1.1% (n = 1)	unrelated
Hyperglycemia	1.1% (n = 1)	unrelated
Preexisting anemia	1.1% (n = 1)	unrelated
Decrease in activated partial prothrombin time	1.1% (n = 1)	possible
Decrease in platelet count	1.1% (n = 1)	unrelated

quite obvious; higher dosages were hemodynamically clearly more effective than the lower dosages. In contrast to hypertension, dose selection is difficult in CHF as there is no documented surrogate end point for morbidity and mortality. Although the hemodynamic effects of LU135252 may be favorable, not all drugs with such effects improved prognosis in CHF (e.g., milrinone, flosequinan) (32-34). The fact that ET correlates with prognosis (15-17), however, strongly suggests that blockade of the system may be clinically important for morbidity and mortality.

Endothelin plasma levels in heart failure. Plasma levels of ET-1 and its precursor, big ET-1, are strong independent predictors of death (16,35). Thus, ET antagonists are of great clinical interest as mortality remains high in patients with CHF in spite of currently available drugs. Endothelin-1 exerts its vasoconstrictive effects through activation of ET_A and ET_B receptors on vascular smooth muscle cells. The ET_A receptor also mediates proliferation of vascular smooth muscle cells (9). In contrast, ET_B receptors on endothelial cells mediate the release of vasodilating and antiproliferative NO and prostaglandins (10-12) and are involved in the clearance of ET-1 (22-25). Indeed, selective ET_B antagonism exerts unfavorable hemodynamic effects (36,37). Therefore, there is particular interest in selective ET_A receptor antagonists as therapeutic agents in chronic heart failure. As in previous studies with other ET-1 receptor antagonists, ET-1 plasma levels increased significantly after administration of the selective ET_A receptor antagonist LU135252, presumably due to displacement of ET-1 from its receptors. However, changes in plasma ET-1 were clearly smaller than those observed after administration of bosentan, a nonselective ET_{A/B} receptor antagonist although the selective ET_A receptor antagonist LU135252 was at least as hemodynamically potent as the combined ET_{A/B} receptor antagonist, both on the arterial and venous side of the circulation (4,19,20,38,39). Thus, the present findings suggest that selective ET_A blockade, which does not interfere with ET_B receptors, does not impair clearance of ET-1 from the human circulation (22-25).

This can have clinical relevance as elevated ET-1 plasma levels in chronic heart failure are, in part, due to down-regulation of lung ET_B receptors with subsequent reduced clearance of ET-1 (40,41). Further, the risk of adverse events after drug withdrawal (e.g., rebound vasoconstriction) seems to be much lower.

Safety and tolerability. The ET_A receptor antagonist LU135252 was generally well tolerated. In this study, there was one episode of pulmonary edema in a patient with markedly elevated pulmonary artery pressure and one episode of hypotension. In a previous study on the hemodynamic effects of another selective ET_A receptor antagonist, BQ-123, an episode of syncope and bradycardia was described, which also occurred in a patient with markedly elevated pulmonary artery pressure (42). Special care may, therefore, be required when starting endothelin antagonists in patients with severe chronic heart failure, as is the case with angiotensin-converting enzyme inhibitors or beta-blockers (43).

Study limitations. This study has several limitations. First, since only short-term hemodynamic and neurohormonal effects were studied, valid conclusions concerning long-term safety and efficacy cannot be drawn yet. Second, for safety reasons, all drugs with impact on hemodynamics were halted before administration of the study drug. Therefore, interactions with other drugs may be more important in daily practice than under the conditions of this study. Third, the study was not placebo-controlled but, rather, compared a wide range of dosages of an active drug (i.e., LU135252). However, in previous studies, placebo did not exert any hemodynamic effects in patients with heart failure under the experimental conditions utilized in these patients (19,20). Also, the striking dose-dependency of the effects of LU135252 on CI and pulmonary vascular resistance strongly argues for a very specific mode of action. To address these limitations, further studies are, therefore, under way.

Summary and conclusions. In summary, this study for the first time shows in a large patient population that the selective ET_A receptor antagonist LU135252 improves hemodynamics in patients with chronic heart failure. Administration of LU135252 was not accompanied by neurohormonal stimulation and caused smaller increases in ET-1 plasma levels than the previously reported nonselective ET_{A/B} receptor antagonists. The results suggest that ET_A receptors are of primary importance for the hemodynamic abnormalities in CHF and support the concept that ET_B receptors play an important role in clearance of ET-1 from the human circulation.

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Reprint requests and correspondence: Dr. Thomas F. Lüscher, Cardiology, University Hospital, CH-8091, Zürich, Switzerland. E-mail: cardiottf@compuserve.com.

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